Chapter 5
Gene-Environment Interaction and Individual Susceptibility to Metabolic Disorders

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5.1 Introduction

Overweight and obesity (see Table 5.1 for definitions), particularly when fat is accumulated in the abdominal area, associate with a number of metabolic complications including hypertension, dyslipidemia, insulin resistance and type 2 diabetes (T2D). The close link to T2D constitutes a particular health threat given the increased risk for cardiovascular disease in diabetes. Worldwide, nearly 40% of the adult population is estimated to be overweight and 10–15% obese [1]. Furthermore, >400 million people worldwide are living with T2D [2], and an additional 10% of the global population are likely to develop the disease. The rapid increase in obesity/T2D is multifactorial but primarily due to life-style including caloric over-supply and sedentary habits. Ongoing urbanization is an important underlying factor [3]. Altogether, this makes understanding of the underlying mechanisms and development of preventive strategies prioritized research areas.

5.2 Genetic Susceptibility to Obesity and T2D

Genetic epidemiological studies have provided support for a strong hereditary impact on obesity and T2D. More recently, progress in genetic techniques has permitted mapping of hundreds of susceptibility (risk) gene loci for these diseases.

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Table 5.1 Classification of body weight. The degree of excess body weight is categorized using Body Mass Index (BMI) which is calculated by dividing the body weight in kilograms with the square of the height in meters. The corresponding value in kg/m^2 is used to categorize individuals as normal weight, over weight and obese

	Body Mass Index (kg/m^2)
Normal weight	18.5– < 25
Overweight	25.0– < 30
Obesity	≥30

Mendelian randomization, in which the risk factor obesity has been replaced by genetic risk loci for BMI, has established a causal link to T2D and coronary artery disease (CAD) [4]. Despite this, most susceptibility gene loci do not overlap between the different traits suggesting that obesity, T2D and CAD develop through distinct mechanisms [5]. This notion is supported by the clinical observation that a proportion of morbidly obese are relatively metabolically healthy [6] and conversely, some patients with T2D are lean. This is also the reason why obesity and T2D are discussed in separate paragraphs in this chapter. Importantly, despite progress in human genetics, for most genetic loci associated with BMI and/or T2D, the underlying causative genes and involved organs remain to be identified. At best, defining genes contributing to obesity and T2D can identify new therapeutic targets. However, there is also an expectation of "precision medicine", i.e. that genetic information can be used to highlight which primary prevention intervention strategies and/or therapies that are most effective in a specific individual.

5.3 The Relationship Between Genetic and Environmental Factors in Obesity and T2D

Life-style modifications are an integral part in obesity prevention/treatment and large randomized control trials (RCTs) have clearly shown that physical activity and dietary interventions can minimize the risk, or delay the onset, of T2D [7]. Furthermore, twin studies support the notion that genetic background influences change in body fat storage in response to dietary intervention [8], and that physical activity decreases the genetic impact on BMI and body fat distribution [9]. Thus, the response to life style factors is the result of an interaction with genetic background, and to design effective prevention and treatment for obesity and T2D it will be necessary to define the most critical causal environmental factors for each individual. For this to become possible researchers must define the interaction between genetic variants and environmental factors. Both obesity and T2D arise from the interactions between a genetic risk profile and obesogenic environmental factors which include not only physical inactivity and excessive caloric intake but may also involve factors such as medications, socioeconomic status, poor sleep quality,

and the gastrointestinal microbiome [4]. Environmental factors may also share mechanisms with gene variants, and studies of gene-environment interactions can potentially highlight pathways underlying genetic susceptibility to disease.

5.4 Genetics of Obesity

Heredity has a substantial impact on obesity which has been confirmed in numerous genetic epidemiological studies. Early twin studies estimated the heritability of BMI, i.e. the proportion of variance in BMI controlled by additive genetic factors, to be between 40–70% [10]. The obesogenic environment underlying the obesity epidemic has not altered the overall heritability for BMI, which has remained unchanged in more recent studies [11].

The genetic causes behind obesity may in theory depend on variations/mutations in single (monogenic obesity) or a combination of genes (polygenic obesity). It is now known that monogenic obesity is a rare condition characterized by early onset severe obesity. The early successes in obesity genetics were obtained in this group of patients and identified causal mutations in several genes (e.g. *MC4R*, *BDNF*, *PCSK1*, *POMC*, *SH2B1*, *LEP*, *LEPR*, and *NTRK2)* implicated in hypothalamic pathways involved in central regulation of food intake and satiety. Studies of monogenic obesity highlighted the leptin–melanocortin pathway as a key regulator of energy intake [12].

Unlike monogenic obesity, the genetic risk of common obesity reflects the accumulation of multiple loci, each contributing a small portion of the total risk (polygenic obesity). Analyzes of multifactorial traits have been revolutionized by the genome-wide association study (GWAS) approach in which a large number of study subjects, cases and controls or a population based cohort, are genotyped for millions of single nucleotide polymorphisms (SNPs) covering the common variation in the genome. The SNPs are individually analyzed for association with the disease or trait of interest. Due to the large number of independent tests, a nominal $P < 5x10^{-8}$ is required for genome-wide significant association of <5%. In 2007, SNPs in the first intron of *FTO* were reported to be associated with BMI [13]. *FTO* remains to date the strongest susceptibility gene locus for common obesity and has been confirmed in multiple studies and ethnic groups. *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase that is ubiquitously expressed but most highly expressed in hypothalamic nuclei governing energy balance [14], and has been reported to affect Leptin signaling [15]. However, the exact mechanisms remain elusive and more recent studies have proposed that SNPs in the *FTO* gene could impact on BMI by controlling the expression of the nearby gene *IRX3* and by influencing the metabolic function of adipocytes [16].

Subsequent GWAS in larger cohorts have identified additional genetic risk loci for BMI. Interestingly, several of the genes in the vicinity of these loci have previously been implicated in monogenic obesity [4]. The most recent and largest meta-analysis encompassing ~500,000 study subjects of mainly European and

Japanese descent brought the total number of BMI-associated loci to >200 [5]. The effect sizes of individual BMI-loci are modest, ~0.06–0.4 kg/m^2 per BMI-increasing allele, with the *FTO* locus having the largest effect. In accordance with the modest effect of individual loci, the joint effect of known BMI loci explain in the order of 3% of the population variance in BMI [5]. As a consequence of the low explanatory power, genetic risk loci or a genetic risk score for BMI based on multiple unique loci are inefficient to predict obesity.

Genes encoded near BMI-associated genetic loci display enriched expression in the central nervous system, suggesting that genetic control of BMI primarily involves control of food intake. Nevertheless, while BMI-associated genetic variants are over-represented for tissue-specific enhancers active in the CNS, they are also present in immune cells and adipose tissue indicating the potential importance of additional cell types/organs for the development of obesity [5].

5.5 Genetics of Body Fat Distribution

An important aspect of body fat mass is the accumulation into different peripheral depots. Expansion of the abdominal subcutaneous and visceral depot is closely associated with metabolic complications. An estimate of body fat distribution is obtained from the waist-to-hip ratio (WHR). A large GWAS meta-analysis in >200,000 study subjects identified 49 loci linked to BMI-adjusted WHR [17]. Genes expressed near these loci are enriched in adipose tissue, suggesting that fat distribution is at least to some degree determined by regulation in the fat depots themselves. While the 49 WHR-loci together explain 1.4% of the population variance in WHR, there is a gender effect as the associations were stronger in women than in men. Importantly, most genetic loci associated with WHR do not overlap with those for BMI, suggesting that genetic variations in fat distribution and total adiposity are mediated via independent mechanisms [4]. Nonetheless, the central roles of the *FTO* and *MC4R* loci for adiposity are strengthened by the finding that these genetic loci are associated with multiple adiposity traits. Studies of gene-environment interaction have mainly focused on genetic loci associated with BMI, and not those exclusively associated with BMI-adjusted WHR. This makes sense since BMI, but not body fat distribution, is strongly influenced by behavioral factors. It is therefore mainly BMI that is discussed below in conjunction with potential factors interacting with genetic susceptibility.

5.6 Genetics of Type 2 Diabetes

The genetic architecture of T2D exhibits great similarities to that of obesity, although a distinct set of genetic risk loci are involved. The heritability of T2D has been calculated to be between 30–35% in genetic epidemiological studies [18]. A few

risk loci for T2D were identified before the GWAS era. These include a locus on chromosome 10 encoding the transcription factor *TCF7L2*, as well as a common variant in the 5′ region of *PPARG* on chromosome 3. In GWAS, around 250 genetic risk loci for T2D have been mapped [19]. Together, these loci explain ~20% of the genetic risk of developing T2D [18]. Analyses of quantitative traits have identified three clusters of susceptibility loci for T2D; the first and largest cluster encodes genes primarily involved in insulin secretion (i.e. *GIPR, C2CDC4A, CDKAL1, GCK, TCF7L2, GLIS3, THADA,* and *IGF2BP2*). The second cluster is primarily associated with insulin sensitivity and encodes genes such as *PPARG*, *KLF14*, and *IRS1*, which encode proteins involved in the peripheral regulation of insulin signaling. The third cluster contains genes such as *NRXN3*, *CMIP, APOE*, and *MC4R* and is associated with BMI and lipid traits [20]. More recent exome sequencing in cases and controls has identified additional rare variants associated with T2D, but most often these are in loci already discovered by GWAS [21].

The chromosome 10 region encoding *TCF7L2* is the locus with strongest impact on the risk of developing T2D. Each risk-allele of *TCF7L2* increases the risk about ~1.3 fold [22]. *TCF7L2* is an effector in the Wnt signaling pathway, which has important functions in proliferation and differentiation processes. *TCF7L2* seems mainly to influence T2D risk by impact on beta cell insulin secretion [23]. However, *TCF7L2* has also been linked to adipogenesis [24] and liver insulin sensitivity [25].

5.7 Gene Environment Interaction

By *gene-environment interaction* we refer to situations with synergistic effects, that is where the joint effect of genotype and environment is less or greater than would be expected if the effect is additive. Numerous gene-environment interaction studies for obesity and T2D have been published. However, many findings have not been possible to reproduce, which has been attributed to small effects and sample sizes yielding low statistical power, as well as failure to account for multiple testing given the many genetic loci and potential environmental factors available for analysis. Herein, we have prioritized results from studies analyzing larger cohorts, even if they may not be the first to report the association with a specific environmental trigger. Furthermore, given that many findings in animal models cannot be translated into humans, we only report results from clinical studies. Most gene-environment studies for obesity and T2D are observational cross-sectional or cohort studies with information about disease incidence during a follow up period after exposure. A few RCTs are also mentioned. These have the advantage of testing the effects of specific environmental factors, while controlling for confounders; the drawback is low power due to limited sample size.

5.8 Gene Environment Interaction in Obesity

5.8.1 Obesogenic Environment

Overall, individuals with the greatest genetic predisposition to obesity seem to be more susceptible when exposed to today's obesogenic environment. This notion is based on several independent observations. Thus, a risk score based on 29 BMI-associated SNPs had stronger effects on BMI in those born more recently [26]. In concordance, studies of the *FTO* locus and high penetrant mutations in the *MC4R* gene have reported a stronger association between risk alleles and BMI in later birth cohorts [27, 28].

So what are the environmental factors that modify the impact of susceptibility gene loci? A comprehensive study based on the UK Biobank showed that a composite score of obesogenic environmental factors is of importance [29]. An index for social deprivation based on work and housing situation accentuates genetic susceptibility to high BMI. Here, the impact on BMI of a genetic risk score comprising 69 SNPs was larger in the group with the most relatively deprived situation. For the half living under the most deprived situations, carrying 10 additional BMI-raising alleles was associated with 3.8 kg extra weight, whereas for the half living under the least deprived situations, carrying 10 additional BMI-raising alleles was associated with 2.9 kg increase in weight. The same study reported interaction between genetic risk and physical activity, sedentary time, or TV watching in predicting BMI of similar effect sizes. Altogether, these analyses suggest that genetic predisposition to obesity is influenced, albeit to a minor degree, by an obesogenic environment.

5.8.2 Diet

A healthier diet is associated with lower BMI [30]. A number of studies have assessed if the diet also influences genetic predisposition to obesity. A genetic risk score comprising BMI-associated SNPs has been reported to be associated with a lower total energy intake as well as higher intake of fiber, but not with relative intake of other macronutrients [31]. By contrast, there seems to be no interaction between genetic risk score and dietary composition on BMI [29–31]. However, a genetic risk score based on WHR-associated SNPs showed nominally significant interaction with a favorable diet i.e. relative higher intake of whole grains, fish, fruits, vegetables, and nuts/seeds [30]. The healthier diet strengthened the association between the genetic risk score and WHR, thus not supporting the hypothesis that healthy diet offset genetic risk. Cooking method could, hypothetically, also influence genetic impact on BMI. Conflicting results have been reported as regards interaction between genetic risk score and intake of fried food in determining BMI [29, 32]. Thus, overall macronutrient intake and cooking method seem to have at most a modest impact on genetic susceptibility to obesity.

As *FTO* is the genetic locus with strongest effect on common obesity, numerous studies have investigated the association and interaction of the *FTO* locus with dietary factors [33]. The BMI increasing *FTO* allele has been reported to be associated with modestly lowered total energy intake and with relative higher dietary protein intake among adults, suggesting that the *FTO* gene could be involved in some aspects of food preference [33]. By contrast, in children and adolescents the BMI-increasing *FTO* allele is associated with increased total energy intake but not with macronutrient composition [34]. Nevertheless, the *FTO* gene variant interacts with protein intake i.e. the association between *FTO* genotype and BMI is stronger in individuals with high protein intake [34]. The *MCR4* gene, another important risk locus for obesity involved in central regulation of food intake, does not seem to associate with total energy or macronutrient composition [33].

Compelling evidence supports a link between the consumption of sugar-sweetened beverages [35] and an increased risk of obesity, and sugar-sweetened beverages may also adversely affect genetic susceptibility. In agreement with this, it has been reported that the effect of a genetic risk score of BMI-associated SNPs is twofold higher in those with the highest (≥1 serving/day) versus lowest (<1 serving/month) intake of sugar sweetened beverages, and the risk of developing obesity was fourfold higher [36]. On the other hand, in the UK Biobank no interaction was observed between consumption of fizzy drinks and a genetic risk score of BMI-associated SNPs on BMI [29]. However, the results are not directly comparable as drink intake was measured and grouped in different ways in the two studies. Intake of other beverages can also modify the association between genetic risk and BMI; increased alcohol intake has been reported to attenuate the association between a genetic risk score and BMI [37], and between *FTO* SNPs and BMI [38]. Thus, whereas intake of sugar-sweetened beverages seems to have an unfavorable impact on BMI in particular among those with a high genetic risk for obesity, this is not the case for alcohol intake.

Genetic susceptibility to obesity can be mediated via control of food intake but also the hedonic effects of food suggesting the potential importance of eating behavior. Eating behavior can be classified as emotional, uncontrolled, or cognitive constraint. A risk score for BMI has been reported to be positively associated with emotional eating behavior [39]. Furthermore, an interaction between cognitive constraint eating behavior and the genetic risk score on BMI was observed. The association was strongest in the lowest tertile of "cognitive constraint" supporting the notion that eating behavior could help to protect genetically susceptible individuals from weight gain.

5.8.3 Physical Activity

Physically active individuals have lower risk of obesity [40]. In genetic epidemiological studies physical activity reduces the genetic influence on BMI [9]. In agreement with this, in the European Prospective Investigation of Cancer (EPIC)-Norfolk

cohort a genetic risk score explained 1.2% of the variation in BMI in the inactive group and 0.6% in the active group [41]. These results have been replicated in a larger meta-analysis [29]. In prospective analysis, the genetic risk score tended to be associated with an increase in annual BMI in physically inactive individuals, whereas the opposite trend was observed in physically active individuals [41].

FTO is not in itself associated with physical activity [40]. However, a protective interaction between *FTO* risk allele and physical activity on body fat and body fat distribution has been reported [40]. In adults, the *FTO* risk allele was associated with an odds ratio (OR) of 1.23 for obesity in the active group, and OR 1.3 in the inactive group, representing a 27% reduced risk of obesity in physically active individuals. No interaction between the *FTO* locus and physical activity on BMI was observed in children and adolescents. The above findings have clinical implications since they support that those with the highest genetic risk for obesity benefit the most from physical exercise.

5.8.4 Effects of Combined Life-Style Modifications in Relation to Genetic Risk

The potential interaction between genetic susceptibility and life style intervention on changes in body weight has been assessed in a few RCTs. Meta-analyses of RCTs including dietary, physical activity or drug-based interventions have not identified any interaction with BMI-associated genetic loci on weight loss outcome [42, 43]. Although of limited size, these RCTs consolidate the results from the epidemiological studies and suggest that life style only to a minor degree modify genetic influence on BMI.

5.8.5 Smoking

Smoking has many negative effects, particularly on lung function and CAD. One reason to continue smoking despite the side effects may be that cessation is associated with weight gain [44]. It is therefore of interest that the impact of specific SNPs associated with BMI or body fat distribution on adiposity has been reported to be dependent on smoking [45]. Besides established pathways underlying genetic susceptibility to obesity, e.g. central regulation of food intake, the genetic loci dependent on smoking implicate additional factors such as nitric oxide synthesis in body fat regulation [45]. The variance in BMI explained by BMI associated-SNPs interacting with smoking was larger among smokers than nonsmokers. By contrast, SNPs interacting with smoking explained a greater proportion of variance in body fat distribution among nonsmokers. These results are potentially clinically important as they suggest that smoking may increase genetic susceptibility to central fat accumulation, but attenuate the genetic effects on BMI. Thus, among subjects

carrying high risk alleles, smoking cessation might have a positive effect on central (abdominal) fat accumulation since the interaction between smoking and risk alleles will no longer be present.

5.8.6 Sleep

All living organisms have a circadian rhythm, i.e. an underlying 24 h physiological cycle for e.g. body temperature and hormones. The "chronotype" is the propensity of an individual to sleep at a particular time during a 24-hour period. The normal variation in chronotype ranges from around two hours earlier to two hours later than average. Furthermore, short and/or poor sleep is associated with obesity and T2D [46, 47]. Genes controlling circadian rhythm are important for chronotype, In addition, chronotype is likely influenced by environmental factors including light, feeding, and social behavior. BMI is genetically associated with chronotype, undersleeping (<7 h), and oversleeping (>8 h) [48]. However, in Mendelian randomization experiments there is no evidence for causality between BMI and sleep pattern. While these results are of interest, no study has to our knowledge investigated if sleep influences genetic impact on BMI.

5.9 Gene Environment Interaction and T2D

Improvement in lifestyle including healthy diet and increased physically activity can reduce the risk of progression to T2D in high-risk individuals by ~50% [7]. Knowledge of whether some individuals display a better response to intervention due to e.g. genetic profile would benefit clinical practice and primary prevention. Consequently, a number of studies have assessed the interaction between genetic risk loci for T2D and life style on incidence of T2D.

5.9.1 Diet

Western diet has been blamed for the recent T2D epidemic whereas the "Mediterranean" diet reduces the risk of developing the disease [49], but do they modify the genetic risk? A synergistic interaction between Western dietary pattern and a T2D genetic risk score on T2D incidence has been reported [50]. Western dietary pattern increases T2D risk among those with a higher, but not among those with lower, genetic risk. By contrast, there seems to be no interaction between a genetic risk score and Mediterranean diet on incident T2D [51]. Nor do specific macronutrients or food items interact with genetic risk for T2D [52]. Gut hormones, such as incretins, are of major importance for T2D pathophysiology and glucose

control. Both genetic variants and dietary factors influence incretin release and function. A significant interaction between coffee consumption and a genetic risk score comprising T2D-associated SNPs in incretin-related genes (*GIPR, KCNQ1, TCF7L2 and WFS1*), as well as *TCF7L2* gene variants on its own, on T2D risk has been reported. Coffee protected against T2D in individuals carrying the *TCF7L2* risk allele [53]. Overall, however, dietary pattern seems to have at most a modest impact on genetic susceptibility to T2D.

5.9.2 Physical Activity

A significant interaction between physical activity and a genetic risk score for T2D, but not individual SNPs, on T2D incidence has been reported [54]. The protective effect of physical activity was weaker among those with a high genetic risk. Interestingly, the interaction was observed for SNPs implicated in regulation of insulin resistance as opposed to insulin secretion, suggesting that the former genes are easier to influence through behavioral changes. However, in even larger studies no interaction between physical activity and genetic risk score on T2D incidence was observed [51]. Furthermore, a genetic risk score was not associated with T2D incidence or regression to normoglycemia in the DPP trial encompassing life style change or pharmacological intervention with Metformin [55]. Thus it is presently unclear whether genetic risk for T2D can be modified by physical activity. Larger studies, also including more recently identified susceptibility gene loci for T2D, may clarify this.

5.10 Limitations

There are several aspects that limit the generalizability of the discussed results. First, the most clinically relevant crossover interactions are situations where someone at high genetic risk of disease in one setting may be protected if environmental exposure improves. However, genetic variants involved in such interactions are unlikely to be detected in GWAS if the environmental trigger is no accounted for, which has usually not been the case, i.e. if a gene allele increases the risk of T2D in one group and reduces the risk of the disease in another group, association between the allele and T2D is difficult to detect unless the group effect is taken into account. Thus, although hundreds of genetic loci associated with BMI, WHR and T2D have been identified, there might be other as yet unidentified loci that display stronger interaction with life style. Second, there is a large heterogeneity in the studies included in the meta-analyses referred to above, and a large bias can be expected in self-reported data. Finally, many reported studies analyze genetic risk scores, which has greater power than individual SNPs for detecting interactions with environmental factors; however, genetic risk scores provides little guidance in identifying specific culprit pathways affected by the environmental factor.

5.11 Conclusions

This chapter has focused on the genetic and environmental interactions in common forms of obesity and T2D. While genetic variations explain a substantial proportion of the heritability, known genetic risk loci can only explain a minor fraction of the inter-individual variations in the two conditions. Environmental factors have a major impact on obesity and to some degree on T2D, but only modulate the genetic influences on disease to a minor degree. As a consequence, despite the high expectations for precision-based medicine there is currently limited (if any) benefits of subdividing subjects according to genetic risk score, at least for interventions aimed against obesity and T2D.

New approaches, such as refining T2D diagnoses into different subgroups with different patient characteristics might improve the power to detect clinically relevant gene –environment interactions, e.g. physical exercise might be most important among the subgroup of T2D patients that are most insulin resistant [56]. More advanced genetic instruments may improve the predictive value and enable precision medicine but these technical approaches must always be compared with simple and cheap assessments such as asking for the body weight of the parents, T2D family history and determining simple anthropometric measures such as BMI and waist circumference. There is certainly a lot to be done in order to improve our understanding of gene-environmental interactions and their pathophysiological role in metabolic disorders.

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